of HPV-associated head and neck squamous cell carcinoma (HNSCC). The efficacy of the irradiation and vaccine association was tested using a model of HNSCC obtained by grafting TC-1/luciferase cells at a submucosal site of the inner lip of immunocompetent mice. Irradiation and the STxB-E7 vaccine acted synergistically with both single and fractionated irradiation schemes, resulting in complete tumor clearance in the majority of the treated mice. A dose threshold of 7.5 Gy was required to elicit the dramatic antitumor response. The combined treatment induced high levels of tumor-infiltrating, antigen-specific CD8(+) T cells, which were required to trigger the antitumor activity. Treatment with STxB-E7 and irradiation induced CD8(+) T-cell memory, which was sufficient to exert complete antitumor responses in both local recurrences and distant metastases. We also report for the first time that a combination therapy based on local irradiation and vaccination induces an increased pericyte coverage (as shown by αSMA and NG2 staining) and ICAM-1 expression on vessels. This was associated with enhanced intratumor vascular permeability that correlated with the antitumor response, suggesting that the combination therapy could also act through an increased accessibility for immune cells. The combination strategy proposed here offers a promising approach that could potentially be transferred into clinical trials. The implementation of selective immunomodulatory approaches during the treatment of HPV positive tumors could eventually lead to increase anti tumor efficacy with favorable tumor versus normal tissue differential effect.

Keywords: HPV, STxB-E7 vaccine, radiation, mice

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How emerging trends in basic research & technology will shape clinical research?

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Radiation therapy is an ever changing discipline and technology. It has made unprecedented improvements with the incorporation of concurrent chemotherapy regimens which translated into local control and survival gains. The improvements of beam delivery techniques have led to decrease in morbidity following treatment. We are now facing an important wave of changing concepts which profoundly impact our understanding of the basic mechanistic of oncology which have had profound consequences on the perception of the biology of response to radiotherapy having both consequences for tumor and normal tissues. Interestingly these changes do not replace former concepts but rather contribute to broaden the scope of radiation biology. Direct radiation induced cell kill of tumor clonogens has now to be integrated within the concept of microenvironment. The overwhelming contribution of tumor hypoxia remains un disputed but the concept of micro environment by itself now implies the contribution of several cellular compartments which are shown to contribute to both tumor response and the generation of normal tissue damage. These findings have paved the way for a new generation of combination of clinical trials which are now emerging. The possibility that immune modulation during the course of radiotherapy could not only have impact on local control but also on distant disease is a fascinating paradigm. Technology for treatment and imaging have in parallel considerably evolved, leading to increased precision and targeting possibilities widening the use of stereotactic radiotherapy which constitutes a major change for the management of primary and secondary tumors. Routine integration of biomarkers in our tumor rounds such as HPV status for head and neck and 1p19q for brain tumors are examples of the integration of the concept of precision medecine into radiotherapy and other examples should follow.
Functional imaging and the latest developments of image texture analysis will contribute to increase the level of precision of our treatments, define the areas at risk for relapse but these images might also contains valuable biological information. Practical examples of clinical trials using novel technologies (nanoparticles), biomarkers selection and oligometastatic disease, will be used to present the practical integration and the challenges represented by these novel concepts into the clinic.

Keywords: Oligometastasis, clinical trial, immune therapy, targeted therapies, biomarkers, functional imaging.

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First tests to implement an in-house 3d-printed photon bolus procedure using clinical treatment planning system data.

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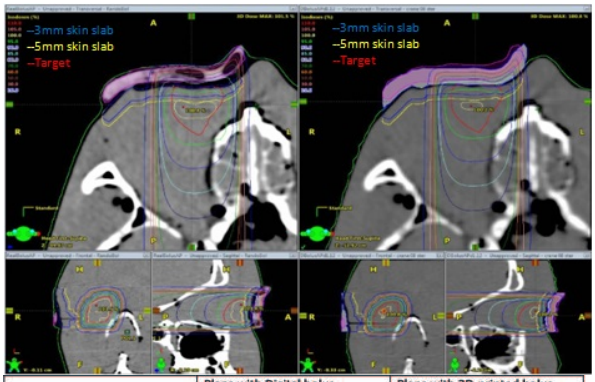
Purpose: Additive manufacturing is becoming of interest in Radiotherapy especially for bolus creation. This study aimed to develop an in-house procedure to print photon bolus created with the treatment planning system (TPS) using small sized printers, cost effective, and logistically easy to implement in RT departments.
Material/methods: A fused deposition modeling (FDM) printer with a heated bed plate (Rova3D, Ordsolutions, Ontario, Canada), was used together with Poly-Lactic-Acid (PLA) material. Using as TPS Eclipse™ version 13 (Varian Medical Systems, Palo Alto, California) a plan was created on a Rando™ head phantom CT scan and a "digital" bolus created in the eye region with Hounsfield Units (HU) of 140, corresponding to PLA printed density of 1.12 g/cc. This bolus was exported from Eclipse and converted in STL file. Bolus creation and printing took approximately 1 hour. To verify the form of the 3D-printed bolus, its HU, and dose distribution obtained when using it, the latter was positioned on the head phantom and a CT scan was acquired. Two plans with anterior-posterior fields and 6 MV X-ray beams were created using either the "digital" or the 3D-printed bolus and plans were compared. To measure and compare the dose distribution, skin layers of 3 mm and 5 mm thickness were created, just beneath the bolus, as well as a target simulating a tumor reaching the body surface (see figure). The analytical anisotropic algorithm was used for dose calculation with a grid size of 1 mm.
Results: The first 3D-printed bolus contained some air bubbles, and had a smaller thickness (less than 0.1 cm) but properly reproduced the form (see figure). The printed bolus presented in its solid portion a density of 140-150 HU with values as low as ≈-450 HU in the bubble regions and a mean ±SD value of -32 ± 154 HU. Dosimetric comparison showed good agreement on mean doses and max doses, while volumes receiving 95% of the prescribed dose differed by ≈6% for all structures with 3D-printed bolus plans showing more coverage, (see table).
Conclusion: In conclusion, first dosimetric results look promising and further tests will be implemented to improve the bolus filling and the erosion of the surface, as well as to investigate the possibility to use soft PLA materials (likely more comfortable for patients). More sophisticated, realistic patient's plans should be tested and *in-vivo* thermo luminescent dosimetry should be used for treatment plan verification.



	Plans with Digital bolus	Plans with 3D-printed bolus
Mean ±Standard Deviation dose %		
Target	97±3	99±3
5mm skin slab	46±42	47±43
3mm skin slab	44±42	45±43
Dnear max (%)		
Target	100	101
5mm skin slab	99	100
3mm skin slab	97	98
Volume receiving 95% dose prescription (%)		
Target	83	89
5mm skin slab	14	20
3mm skin slab	7	13

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Differential cross sections measurements for hadrontherapy: 50 MeV/n ^{12}C reactions on H, C, Al, O and ^{nat}Ti targets.

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The increasing interest for hadrontherapy can be attributed to the great accuracy of ion beams to target the tumor while sparing the surrounding healthy tissues (due to the high dose deposition in the Bragg peak and the small angular scattering of ions) as well as the potential biological advantage of ions for some tumor types compared to photons.
To keep the benefits of carbon ions in radiotherapy, a very high accuracy on the dose location is required. The dose deposition is affected by the fragmentation of the incident ions that leads to: (i) the consumption of the projectiles with their penetration depth in the tissues, (ii) the creation of lighter fragments having a different biological effectiveness (RBE), (iii) the apparition of a fragmentation tail after the tumor. The constraints on nuclear models and/or fragmentation cross sections in the energy range used in hadrontherapy (up to 400 MeV/n) are not yet sufficient to reproduce the local dose deposition with the accuracy required in a clinical treatment.
In this context, two experiments with 95 MeV/n ^{12}C beams have been performed by our collaboration in 2011 and 2013 at GANIL [1,2] to measure the energy and angular differential fragmentation cross sections on thin targets of medical interest (H, C, Al, O and ^{nat}Ti). In March 2015, a new experiment with a 50 MeV/n ^{12}C beam on the same targets has been conducted at GANIL. The experimental set-up was made of five three stages telescopes, each composed of two Si detectors and one CsI scintillator mounted on rotating stages to cover angles from 3° to 39°.
The analysis of this new experiment is under completion. It shows that the angular cross sections for light fragments are less forward-focused at 50 MeV/n compared to 95 MeV/n, resulting in "flatter" distributions. As shown in Figure 1, protons and ^{4}He fragments are dominant on the entire angular distribution. At this beam energy, the production of alpha particles is higher than protons for angles up to 20° compared to 10° at 95 MeV/n.
However, at the most forward angles, ^{11}B fragments seem to compete with the protons production.
The energy distributions of the fragments at forward angles are peaked close to the beam energy showing an emission dominated by the quasi-projectile. Comparisons between experimental data and Geant4 simulations using different inelastic models (such as BIC, QMD and INCL++) show important discrepancies.
Final data as well as comparisons with simulations and the previous experiments will be presented during the conference.

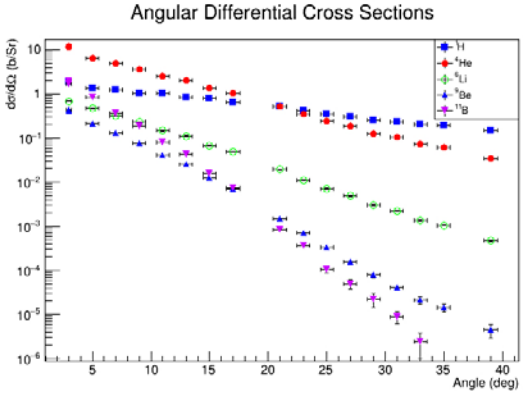

Figure 2: Preliminary angular differential cross section for various isotopes, from Z=1 to Z=5

Keywords: Hadrontherapy, Nuclear-Fragmentation, Cross-Sections

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Correlation of Particle Traversals with Clonogenic Survival Using Cell-Fluorescent Ion Track Hybrid Detector

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Purpose: In radiobiology, the clonogenic survival of cells is considered the gold standard assay for assessment of cellular sensitivity to ionizing radiation. Towards further development of next generation biodosimeters in particle therapy, cell-fluorescent ion track hybrid detector (Cell-FIT-HD) previously engineered by our group [1, 2] was utilized to study its feasibility as a tool for investigating the effects of clinical beams on cellular clonogenic survival.
Materials and methods: Tumor cells were grown on the fluorescent nuclear track detector (FNTD) in cell culture, mimicking the standard procedures for clonogenic assay. Cell-FIT-HD was used to detect the spatial distribution of particle tracks within colony-initiating cells. The physical data were associated to radiation induced foci as surrogates for DNA double strand breakages (DSB), the hallmark of radiation -induced cell lethality. Long-term cell fate was monitored to determine the ability of cells to form colonies.
Results and conclusion: We showed that single cells can attach and grow as colonies on FNTD surface. Usage of the fluorescent and confocal microscopy, together with FNTD technology, enabled simultaneous analysis of the microscopic beam parameters together with the molecular events within colonies, at sub-cellular level. We report the first successful